

## Life-course Smoking Trajectories and Risk of Emphysema in Middle Age: The CARDIA Lung Study

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### Author Contributions

ARM contributed to study conception and wrote the first draft of the manuscript. LAC analyzed and interpreted the data and revised the manuscript. SPB, NA, DRJ, RA, RW, and MTD interpreted the data and revised the manuscript. BH contributed to study conception, interpreted the data, and revised the manuscript. GRW supervised data collection, interpreted the data, and revised the manuscript. RK conceived the study, supervised data collection, interpreted the data,

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*To the Editor:*

Limited long-term prospective data are available to characterize the impact of low rate smoking on lung health outcomes, particularly in population-based cohorts. Prior studies have also differed in measurement of cumulative smoking exposure, with many studies relying on imprecise measurement and long periods of retrospective reporting. Smoking exposure is traditionally indexed by pack-years, and individuals with lifetime smoking thresholds below 10 pack-years are typically excluded from clinical trials for chronic lung disease. However, recent studies have found smoking duration (i.e., years of cigarette smoking) to be superior to cigarettes per day or pack-years in predicting emphysema (1) and mortality (2). Low rate smoking is increasingly prevalent, with 25% of smokers in the U.S. currently consuming fewer than 10 cigarettes per day, and a growing body of literature has identified negative health effects associated with low rate smoking, including cardiovascular disease, cancer, and all-cause mortality (2-4). Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, we studied how longitudinal patterns of smoking exposure – based on cigarettes per day reported annually over 25 years of follow-up – are associated with loss of lung function, incident obstructive lung physiology, and CT-measured emphysema.

**Methods**

CARDIA is a prospective cohort study of the evolution of cardiovascular disease risk factors in 5115 young adults initiated in 1985 (5). Participants were invited to complete follow-up exams at Years 2, 5, 7, 10, 15, 20, 25, and 30 with 91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71% retention. Cigarette smoking was evaluated during each in-person CARDIA visit and at annual phone assessments. We used group-based zero-inflated Poisson (ZIP) trajectory modeling (SAS PROC TRAJ) to identify distinct patterns of smoking among participants, by including all

ever smokers who had data recorded on number of cigarettes smoked per day for at least 3 of the 26 annual queries taken from Year 0 to Year 25 (6). Trajectories of cigarettes/day were specified as a function of participant age using third-order polynomials for both the cigarettes/day Poisson count model and the logit model for predicting extra zeros.

Incident obstructive lung physiology was defined as having a post-bronchodilator forced expiratory volume in 1 second ( $FEV_1$ ) / forced vital capacity (FVC) ratio < 70% at the Year 30 examination but not at the time of peak lung function. Emphysema at Year 25 was determined by visual review of CT scans (7).

We examined the associations of each lifetime smoking trajectory group with lung function decline and risk of future lung disease, relative to never-smokers. Logistic regression models examined smoking trajectory group as a predictor of emphysema on the Year 25 CT scan and Year 30 obstructive lung physiology, adjusting for age, race-sex group, center, height, BMI, physician-confirmed asthma, baseline cigarettes per day, and baseline pack-years.

## Results

Life-course smoking trajectories are presented in Figure 1. Although the Bayesian Information Criterion (BIC) indicated a slightly better fit of the seven- versus six-group model, visual inspection of the trajectory group plots suggested greater parsimony in the six-group model presented below. Trajectory group membership was associated with lung function decline in a stepwise manner by smoking exposure, with heavy stable smokers showing the greatest decline in  $FEV_1$  (-42.2 mL/year; Table 1). Smoking trajectory groups differed in risk of incident obstructive lung physiology, with heavy stable smokers vs. never-smokers demonstrating nearly eight times the odds of obstructive disease and more than twenty times the odds of CT emphysema (Table 1). Among the two low rate smoking groups (low rate stable smokers and

quitters), quitters showed less FEV<sub>1</sub> decline (-33.8 mL/year vs. -35.7 mL/year) and lower emphysema odds than low rate stable smokers despite having greater mean lifetime pack-years (9.8 vs. 6.4, using 20 cigarettes per pack).

## Discussion

In a longitudinal, community-based study, we identified a dose-response relationship of smoking exposure with lung function decline and lung disease risk. Trajectory analyses indicated distinct patterns of life-course smoking, which were differentially associated with lung disease risk. Among the two low rate groups, quitters preserved more lung function and reduced their lung disease risk, relative to low rate stable smokers. These results highlight that there is no safe threshold of sustained smoking with regard to lung disease risk.

The current manuscript extends prior findings on the utility of smoking duration as a predictor of lung health outcomes. Measurement of smoking using pack-years is imprecise (8) and raises concerns of inaccurate reporting and recall bias, especially for individuals whose smoking rate is low or fluctuating. Years smoking may be a more sensitive, reliable, and efficient operational index of smoking exposure in predicting lung disease risk.

Our findings add to a growing body of research on associations between smoking duration and disease risk (2). We identified marked increases in lung disease risk among ever versus never smokers – even among low rate stable smokers, for whom there was nearly three times the risk of incident obstruction and more than an eight-fold increase in CT emphysema risk. As missing data was more common among participants with greater smoking exposure, our analyses are biased toward the null, and effect sizes likely underestimate the true disease risk among heavy smokers. Further, while our approach adjusted for participant-level peak lung

function, we were unable to examine the main effect of peak lung function on subsequent disease risk.(9, 10)

Given that an increasing proportion of individuals smoke at a low or intermittent rate (3), our findings have important public health implications. As compared to never-smokers, low rate smokers demonstrated increased disease risk, despite a relatively low threshold of lifetime smoking exposure (6.4 pack-years). Targeted messaging is needed to reiterate the lung health risk of sustained smoking at any level. Additionally, healthcare providers should underscore the lung health benefit of smoking cessation over and above smoking reduction (i.e., cutting down on cigarettes per day without intention to quit). Although smoking reduction may be a positive initial step toward cessation, prospective studies demonstrate limited lung health benefits of smoking reduction alone (11). This is likely due to changes in smoking topography, in which smokers inhale more deeply and/or smoke more puffs of each cigarette to compensate for a lower number of cigarettes per day. Our findings are consistent with the message that quitting, and not cutting down, is the most effective method of reducing lung disease risk.

Smoking influenced lung disease risk in a dose-dependent manner. There was no safe threshold for smoking intensity on lung disease risk and even low-rate smokers were at increased risk for future lung disease. These results underscore the benefit of complete abstinence from smoking even among low rate smokers on respiratory outcomes.

**Table 1. Smoking trajectory group, mean FEV1 decline, and association (covariate adjusted odds ratio) with incident lung disease**

| Smoking Trajectory Group | FEV <sub>1</sub> decline, mL/year (SEM) | Incident Lung Disease                       |  |                                      |                                   |  |
|--------------------------|---|---|--|--------------------------------------|-----------------------------------|--|
|                          |   | Pre-bronchodilator Obstructive, OR (95% CI) | Post-bronchodilator Obstructive, OR (95% CI) | Centrilobular Emphysema, OR (95% CI) | Paraseptal Emphysema, OR (95% CI) | Any Emphysema (Paraseptal or Centrilobular), OR (95% CI) |
| Never smokers            | -32.48 (0.35)                           | 1.0 (ref)                                   | 1.0 (ref)                                    | 1.0 (ref)                            | 1.0 (ref)                         | 1.0 (ref)  |
| Minimal smokers          | -32.34 (0.53)                           | 1.36 (0.98, 1.88)                           | 1.42 (0.86, 2.35)                            | 1.81 (0.64, 5.15)                    | 1.59 (0.62, 4.09)                 | 1.44 (0.66, 3.13)  |
| Low rate stable smokers  | -35.70 (0.83)                           | 2.44 (1.59, 3.72)                           | 2.80 (1.55, 5.06)                            | 9.60 (4.04, 22.84)                   | 11.24 (5.42, 23.31)               | 8.45 (4.52, 15.82)                                       |
| Quitters                 | -33.80 (0.93)                           | 1.19 (0.69, 2.03)                           | 2.03 (1.02, 4.06)                            | 5.85 (2.13, 16.04)                   | 3.79 (1.46, 9.87)                 | 3.44 (1.53, 7.71)  |
| Moderate stable smokers  | -38.46 (0.87)                           | 3.15 (2.06, 4.81)                           | 5.34 (3.10, 9.19)                            | 25.72 (11.63, 56.88)                 | 21.27 (10.59, 42.73)              | 20.10 (11.15, 36.22)                                     |
| Heavy stable smokers     | -42.19 (1.12)                           | 4.20 (2.52, 6.98)                           | 7.44 (3.94, 14.06)                           | 37.56 (15.87, 88.89)                 | 25.37 (11.68, 55.18)              | 26.01 (13.36, 50.63)                                     |
| Heavy declining smokers  | -41.29 (1.97)                           | 3.04 (1.36, 6.76)                           | 7.54 (2.92, 19.47)                           | 35.53 (11.33, 111.38)                | 26.98 (9.25, 78.70)               | 25.40 (9.82, 65.67)                                      |

*Note.* FEV<sub>1</sub> decline values reflect mean (SE) adjusted annualized decline in lung function from peak measurement to Year 30. Incident lung disease values reflect odds ratios (OR) and 95% confidence intervals (in parentheses). Never smokers were the reference group for all models. Obstructive lung disease indicates FEV<sub>1</sub>/FVC value < 70% at the Year 30 examination but not at the time of peak lung function.

Covariates: baseline age, race-sex group, center, height, baseline BMI, physician-confirmed asthma, baseline cigarettes per day, and baseline pack-years.

## Figure Legend

**Figure 1. Lifetime smoking trajectories by cigarettes per day reported annually over 25 years.** Group-based trajectory modeling was used to generate trajectories of lifetime cigarette smoking. Group compositions were as follows: Heavy declining smokers (4·7%, n=125, mean lifetime cumulative pack-years 38·2), Heavy stable smokers (15·3%, n=406, mean lifetime cumulative pack-years 28·2), Moderate stable smokers (18·4%, n=488, mean cumulative pack-years 15·5), Quitters (12·4%, n=327, mean cumulative pack-years 9·8), Low rate stable smokers (15·9%, n=420, mean cumulative pack-years 6·4), Minimal smokers (33·3%, n=881, mean cumulative pack years 2·1).



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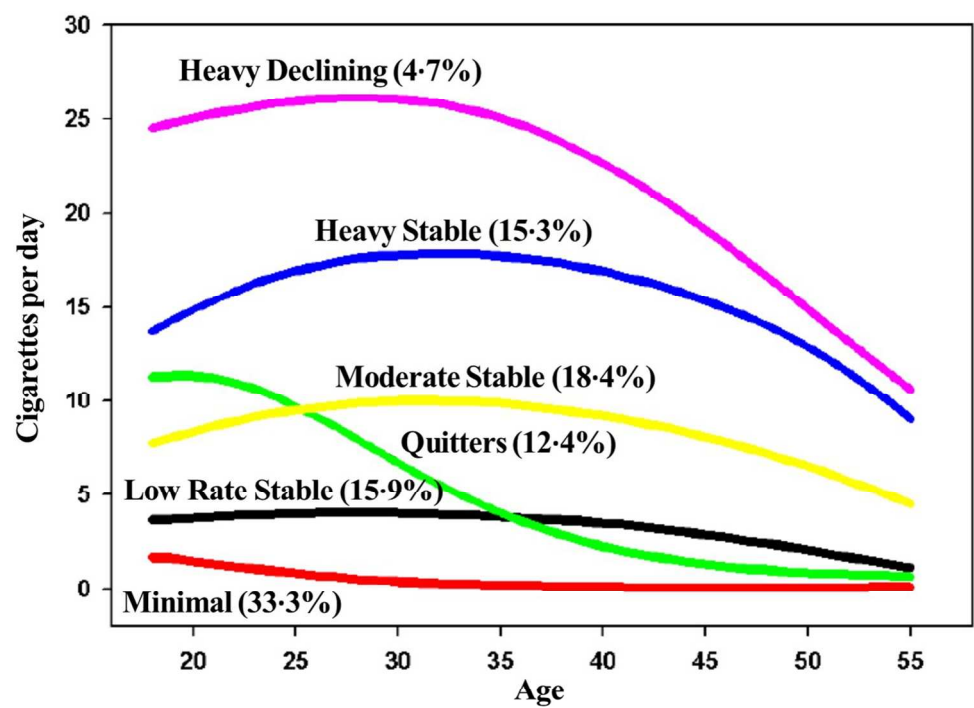


Figure 1

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